Nailfold videocapillaroscopic and other clinical risk factors for digital ulcers in systemic sclerosis: a multicenter, prospective cohort study

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Abstract: OBJECTIVE: To identify nailfold videocapillaroscopic and other clinical risk factors for new digital ulcers (DUs) in a 6-month period in patients with systemic sclerosis (SSc), the videoCAPillaroscopy (CAP) study. METHODS: Overall 623 patients with SSc from 59 centers (14 countries) were stratified into two groups: "DU History" and "No-DU History". At enrollment, patients underwent detailed nailfold videocapillaroscopic evaluation and an assessment of demographics, DU status, and clinical and SSc characteristics. Risk factors for developing new DUs were assessed using univariable and multivariable logistic regression analyses. RESULTS: Of the "DU History" group (n = 468), 79.5% were female, the mean age was 54.0 ± 13.7 years, 59.8% had limited cutaneous SSc, and 22% developed a new DU during follow-up. The strongest risk factors for new DUs identified by multivariable logistic regression (MLR) in the "DU History" group included: mean number of capillaries/mm in the middle finger of the dominant hand, number of DUs (0, 1, 2, 3), and presence of critical digital ischemia. The receiver operating characteristic area under the curve (ROC-AUC) (95% confidence interval [CI]) of the final MLR model was 0.738 (0.681-0.795). Internal validation through bootstrap generated a ROC-AUC (95% CI) of 0.633 (0.510-0.756). CONCLUSION: This international, prospective study including detailed nailfold videocapillaroscopic evaluation and extensive clinical characterization of patients with SSc identified the mean number of capillaries/mm in the middle finger of the dominant hand, number of DUs and presence of critical digital ischemia at enrollment as risk factors for the development of new DUs. This article is protected by copyright. All rights reserved.

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Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis

A Multicenter, Prospective Cohort Study

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Objective. **To identify nailfold videocapillaroscopic features and other clinical risk factors for new digital ulcers (DUs) during a 6-month period in patients with systemic sclerosis (SSc).**

Methods. **In this multicenter, prospective, observational cohort study, the videoCAPillaroscopy (CAP) study, we evaluated 623 patients with SSc from 59 centers (14 countries). Patients were stratified into 2 groups: a DU history group and a no DU history group. At enrollment, patients underwent detailed nailfold videocapillaroscopic evaluation and assessment of demographic characteristics, DU status, and clinical and SSc characteristics. Risk factors for developing new DUs were assessed using univariable and multivariable logistic regression (MLR) analyses.**

Results. **Of the 468 patients in the DU history group (mean ± SD age 54.0 ± 13.7 years), 79.5% were female, 59.8% had limited cutaneous SSc, and 22%**

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developed a new DU during follow-up. The strongest risk factors for new DUs identified by MLR in the DU history group included the mean number of capillaries per millimeter in the middle finger of the dominant hand, the number of DUs (categorized as 0, 1, 2, or ≥3), and the presence of critical digital ischemia. The receiver operating characteristic (ROC) of the area under the curve (AUC) of the final MLR model was 0.738 (95% confidence interval [95% CI] 0.681–0.795). Internal validation through bootstrap generated a ROC AUC of 0.633 (95% CI 0.510–0.756).

Conclusion. **This international prospective study, which included detailed nailfold videocapillaroscopic evaluation and extensive clinical characterization of patients with SSc, identified the mean number of capillaries per millimeter in the middle finger of the dominant hand, the number of DUs at enrollment, and the presence of critical digital ischemia at enrollment as risk factors for the development of new DUs.**

Systemic sclerosis (SSc) is a rare multisystem connective tissue disease characterized by microvascular damage, fibrosis of the skin and internal organs, and specific immunologic abnormalities. Digital ulceration, which represents a visible manifestation of peripheral vasculopathy, is a frequent complication of SSc, with an estimated lifetime prevalence of as much as 50% (1,2).

Digital ulcers (DUs) often occur relatively early in the course of the disease, causing severe pain and functional impairment, and have a great impact on patients' quality of life (3–11). DUs can also result in significant disfigurement and infection and may lead to gangrene, osteomyelitis, and eventually, amputation (4). Furthermore, DUs are often persistent, recurrent, and slow to heal, requiring considerable resources for wound management and nursing care (2,12). Given the clinical and financial burden, as well as the availability of therapies to prevent DUs in patients with SSc (13), there is a need to identify risk factors for the development of new DUs. In addition to the established role of capillaroscopy in the diagnosis of SSc (14–16) and the evaluation of its possible role in monitoring SSc, some studies have reported that abnormalities noted on capillaroscopy are associated with DUs (17–25).

The aim of this study was to identify potential risk factors for the occurrence of new DUs during a 6-month period in patients with SSc, based on nailfold videocapillaroscopy (NVC) findings and other clinical characteristics.

PATIENTS AND METHODS

Study design. The videoCAPillaroscopy (CAP) study was a multicenter, prospective, observational cohort study with stratified enrollment into DU history and no DU history groups. Potential risk factors for the development of DUs were evaluated in the DU history group. The no DU history group was included for exploratory purposes only, as the incidence of new DUs was expected to be low. Enrollment occurred over a 1-year period to minimize seasonal effects. Patients were monitored from the time of enrollment until the occurrence of a new DU or a maximum of 6 months, whichever came first. At enrollment, patients were provided with an educational leaflet on the identification of DUs, and staff at each center telephoned patients monthly to inquire about the occurrence of new DUs. If a DU was reported, a patient visit was organized so that the physician could confirm or exclude the presence of a DU.

Data management was performed centrally, and data quality was rigorously monitored. Consistency of the source data with the clinical database was verified for critical variables for 3 randomly selected patients per site (or fewer, if fewer patients had been enrolled). Data were reviewed regularly.

The CAP study was led by an independent steering committee (see the Supplementary Materials, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). The complete list of CAP study investigators is also given in the Supplementary Materials. This study was conducted in accordance with the Declaration of Helsinki and its amendments, followed the Guidelines for Good Clinical Practice of the International Conference on Harmonisation, and was approved by the local institutional review boards and ethics committees. All patients provided written informed consent.

Study population. Fifty-nine SSc centers in 14 countries (12 European countries and Turkey and Israel) participated in the study between January 31, 2011 and July 26, 2012. Patients ages ≥18 years with a diagnosis of SSc according to the American College of Rheumatology (ACR) (26) and/or the LeRoy and Medsger (14) criteria were eligible for inclusion. The inclusion criteria were broad to permit generalizability to a wider SSc population. To enrich for the occurrence of new DUs in the study population, the patients had to meet 1 of the following 2 criteria: 1) a history of DUs or a DU at enrollment (DU history group), or 2) a disease duration of ≤2 years (no DU history group), defined as the time since the first physician-documented non–Raynaud's phenomenon clinical feature of SSc (3).

As the study was conducted to allow for extrapolation of the results to the real-world setting, patients were permitted to continue their ongoing treatments. Patients unable to undergo NVC assessment were not eligible for study inclusion. Patients with SSc sine scleroderma were excluded as they were not expected to develop DUs frequently during the 6-month observation period. Furthermore, patients who had undergone stem cell transplantation or had participated in an interventional clinical trial within 3 months prior to enrollment were excluded since these interventions may have unknown effects on the occurrence of new DUs.

Data collection. Covariables of demographic features, SSc clinical characteristics, DUs, and other clinical characteristics, as well as findings of the NVC were collected at enrollment and are summarized in Table 1 and Supplementary Tables 1–4 (non-NVC covariables) and in Table 2 and Supplementary Tables 5 and 6 (NVC covariables) (Supplementary Materials are available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). Covariables of DU characteristics included a

history of DUs (assessed at the investigator's discretion), the presence of DUs (number and location), and previous and current DU-associated complications/interventions, including critical digital ischemia (defined as a prolonged, severe, persistent reduction in digital tissue perfusion without rewarming [see Supplementary Table 7 and Supplementary Figure 1]).

Information on medication use within 3 months prior to enrollment, at enrollment, and during the observation period was recorded as predefined classes of medications, including vasoactive medications and immunosuppressants.

Study outcome. A DU was defined clinically as a denuded area located on the fingers and with a defined border and loss of epithelialization and a loss of epidermis and dermis. The definition excluded fissures, paronychia, pitting scars, or ulcers located over the metacarpophalangeal joints or elbows (see Supplementary Table 7, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). DUs distal to the metacarpophalangeal joint and on the volar and dorsal aspects of the hand were included (see Supplementary Figure 1). Calcinosis-induced ulcers were not specifically excluded.

A patient's DU outcome was recorded as a binary variable: either the occurrence or nonoccurrence of a new DU. Cases were defined as patients who experienced a new DU that was confirmed by the investigator during the 6-month observation period. Noncases were defined as patients who did not experience a new DU during the 6-month observation period. For noncases, the nonoccurrence of a new DU was recognized only if the patient had been contacted successfully by staff for at least 3 of the monthly phone calls, including the month 6 phone call, and had reported no new DUs or if the noncases had reported a new DU that had not been confirmed by the investigators. Physicians assessing the presence of DUs were not blinded to the data collected at enrollment.

Collection and assessment of the NVC images. The nailfolds of the second, third, fourth, and fifth fingers of both hands were examined in each patient with the use of a videocapillaroscope equipped with a 200× magnification lens, which is commonly used for NVC (5,27,28), and connected to image analysis software. Two adjacent fields extending over 1 mm, in the middle of the nailfold, and corresponding to the distal row of capillaries were studied (27). Images were evaluated using qualitative and quantitative assessment techniques (18,27,29).

Qualitative assessment of images (1 covariable) (see Supplementary Table 6) classified the patient as having the normal, early, active, or late scleroderma NVC pattern according to Cutolo et al (29) (see Supplementary Materials, Investigator booklet, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). Quantitative assessment of images (6 covariables in each of the 8 fingers) consisted of counting the following 5 covariables per linear millimeter: capillaries, giant capillaries (hairpin-shaped or horseshoe-shaped, homogenously large capillary with a diameter >50 μm), irregularly enlarged capillaries (diameter >20 μm; morphology can be hairpin-shaped, tortuous, or crossing once), microhemorrhages (dark masses due to hemosiderin deposits, which can be linked to a disappearing capillary), and neoangiogeneses (meandering, ramified, branching, bushy, bizarre capillaries and capillaries with >2 crossings), plus a sixth covariable consisting of measuring the maximal capillary diameter in capillaries with a diameter >50 μm (see Supplementary Materials, Investigator booklet).

To ensure optimal reliability in the assessment, staff at all centers had been trained on the assessment of capillaroscopic images in an interactive workshop with practical use of the capillaroscopy devices and were provided with a booklet containing illustrated definitions of the capillaroscopic features (see Supplementary Materials, Investigator booklet). To reflect real-world clinical practice in this observational study, the images were analyzed at each participating center. Picture quality was evaluated for the first 2–3 patients at each center by 3 members of the steering committee (MC, ALH, and VS). If the picture quality was not optimal, further training on the correct use of NVC was provided.

Statistical analysis. *Sample size.* Sample size was based on feasibility considerations, where 350 patients enrolled in the DU history group would provide a reasonable number of cases (n = 150) for model building using a stagewise process to explore risk factor associations and discrimination (30–32). Exploratory statistical analyses were planned for 150 patients in the no DU history group, where the number of cases was expected to be low. Stratification was used to increase homogeneity within the DU history and no DU history groups, because the factors associated with the occurrence of new DUs in the two groups were expected to be different.

Analysis of risk factors for the occurrence of new DUs. Covariables were described for cases and noncases using summary statistics. Associations between the individual categorical covariables and new DU outcomes were initially explored using chi-square test or Fisher's exact test, as appropriate. Summary statistics were provided for continuous variables within the case and noncase groups and for the differences between the 2 groups. Logistic regression modeling was the main analytical method for examining the associations and discriminatory ability of potential risk factors for the occurrence of new DUs, including linear and quadratic functional relationships. The strength of association between a risk factor and new DU outcome was given by the odds ratio (OR) with its 95% confidence interval (95% CI); statistical significance was given via Wald's chi-square test. Model calibration in the multivariable logistic regression (MLR) analysis was assessed via the Hosmer-Lemeshow chi-square test. The discriminatory performance of the various risk factors (individually and combined) was given by the receiver operating characteristic (ROC) area under the curve (AUC) and its corresponding 95% CI.

The statistical strategy for selecting the best-performing risk factors for the final MLR model was a stagewise process in 3 broad stages using "bundles" of covariables (33,34) (see Supplementary Tables 1–6), where stage 1 is univariable logistic regression (ULR) analysis, stage 2 is MLR within-bundle analysis, and stage 3 is MLR across-bundles analysis. The number of covariables was reduced at each stage, and the best-performing covariables from the bundles were carried forward to the next stage.

The non-NVC covariables with similar characteristics (according to the domains on the case report forms) were organized into 4 bundles: bundle 1 for demographics, bundle 2 for SSc clinical characteristics, bundle 3 for DU characteristics, and bundle 4 for other clinical characteristics. Six sub-bundles of NVC covariables (bundles 5.1–5.6) were derived in various ways from the 6 assessed covariables for the 4 fingers on each hand. The NVC sub-bundles were organized on 3 levels for building competing MLR models: the patient, hand, and finger levels (see Supplementary Table 5). The 1 NVC pattern qualitative covariable was used in an alternative final model as a surrogate for the NVC quantitative covariables. Bundle 6 was formed for statistical investigation of interactions between covariables, which were prespecified by

Table 1. Non–nailfold videocapillaroscopy covariables selected at the ULR analysis stage and carried forward to the MLR within-bundle analysis in the DU history group*

Variable	Summary statistics: Cases (n = 103)	Summary statistics: Noncases (n = 365)	ULR: Parameter	ULR: Coefficient estimate (SE)	ULR: OR (95% CI)	ULR: *P*†	ULR: ROC AUC (95% CI)
Demographic features (bundle 1)							
Age at enrollment, mean ± SD years‡	51.5 ± 13.9	54.8 ± 13.6	Intercept	−0.3343 (0.4434)	0.983 (0.967–0.999)	0.033	0.573 (0.509–0.636)
			Linear	−0.0175 (0.0082)			
Currently smoking, n/N (%)	21/103 (20.4)	49/365 (13.4)	Intercept	−1.3490 (0.1239)	1.652 (0.938–2.909)	0.082	0.535 (0.492–0.578)
			Factor	0.5017 (0.2888)			
Comprehensive smoking index, mean ± SD; n§	0.1 ± 0.2; 99	0.1 ± 0.3; 351	Intercept	−1.3697 (0.1332)	¶	0.032	0.535 (0.480–0.590)
			Linear	4.5275 (1.9283)			
			Quadratic	−6.2329 (2.9057)			
SSc clinical characteristics (bundle 2)							
Age at first physician-documented non-RP clinical feature, mean ± SD years; n‡	43.1 ± 14.8; 103	45.6 ± 13.6; 363	Intercept	−0.6748 (0.3734)	0.987 (0.971–1.003)	0.106	0.561 (0.496–0.626)
			Linear	−0.0132 (0.0082)			
SSc subtype, n/N (%)							
Diffuse cutaneous	48/103 (46.6)	140/365 (38.4)	Intercept	−1.0704 (0.1673)	0.713 (0.459–1.108)#	0.133#	0.541 (0.487–0.596)
Limited cutaneous	55/103 (53.4)	225/365 (61.6)	Factor	−0.3383 (0.2249)			
MRSS, mean ± SD; n	13.0 ± 9.0; 100	11.3 ± 8.4; 354	Intercept	−1.5363 (0.1955)	1.023 (0.998–1.048)	0.076	0.562 (0.496–0.627)
			Linear	0.0224 (0.0127)			
Kidney involvement: SSc renal crisis, kidney failure, n/N (%)‡	2/103 (1.9)	22/365 (6.0)	Intercept	−1.2226 (0.1132)	0.309 (0.071–1.336)	0.116	0.520 (0.502–0.539)
			Factor	−1.1746 (0.7470)			
Heart involvement, n/N (%)‡	22/103 (21.4)	55/365 (15.1)	Intercept	−1.3421 (0.1248)	1.531 (0.882–2.658)	0.130	0.532 (0.488–0.575)
			Factor	0.4261 (0.2814)			
Joint involvement, n/N (%)	45/103 (43.7)	127/365 (34.8)	Intercept	−1.4118 (0.1464)	1.454 (0.932–2.269)	0.099	0.545 (0.491–0.599)
			Factor	0.3743 (0.2270)			
DU characteristics (bundle 3)							
No. of DUs, n/N (%)‡							
0 DUs	41/103 (39.8)	262/365 (71.8)					
1 DU	24/103 (23.3)	57/365 (15.6)	Intercept	−1.8548 (0.1679)	2.691 (1.507–4.803)**	<0.001**	0.678 (0.622–0.734)
			Factor	0.9898 (0.2957)			
2 DUs	16/103 (15.5)	27/365 (7.4)	Factor	1.3315 (0.3574)	3.787 (1.879–7.630)††	<0.001††	
≥3 DUs	22/103 (21.4)	19/365 (5.2)	Factor	2.0014 (0.3554)	7.399 (3.687–14.848)‡‡	<0.001‡‡	
Previous complications, n/N (%)							
Soft tissue infection requiring antibiotics	52/103 (50.5)	142/361 (39.3)	Intercept	−1.4708 (0.1553)	1.594 (1.027–2.475)	0.038	0.557 (0.503–0.612)
			Factor	0.4663 (0.2245)			
Autoamputation‡	13/103 (12.6)	14/365 (3.8)	Intercept	−1.3610 (0.1182)	3.621 (1.644–7.977)	0.001	0.544 (0.510–0.578)
			Factor	1.2869 (0.4029)			
Critical digital ischemia	35/103 (34.0)	94/362 (26.0)	Intercept	−1.3752 (0.1357)	1.473 (0.920–2.358)	0.107	0.540 (0.489–0.592)
			Factor	0.3873 (0.2401)			
Gangrene	16/103 (15.5)	37/365 (10.1)	Intercept	−1.3271 (0.1206)	1.630 (0.866–3.068)	0.130	0.527 (0.489–0.565)
			Factor	0.4888 (0.3226)			
Complications at enrollment, n/N (%)							
Soft tissue infection requiring antibiotics	23/99 (23.2)	24/311 (7.7)	Intercept	−1.4499 (0.1242)	4.085 (2.194–7.606)	<0.001	0.579 (0.536–0.621)
			Factor	1.4073 (0.3171)			
Critical digital ischemia‡	15/99 (15.2)	12/311 (3.9)	Intercept	−1.3891 (0.1191)	5.014 (2.266–11.094)	<0.001	0.556 (0.521–0.592)
			Factor	1.6122 (0.4052)			
Previous DU-associated interventions, n/N (%)							
Hospitalization for DU	55/103 (53.4)	144/365 (39.5)	Intercept	−1.5268 (0.1592)	1.759 (1.132–2.732)	0.012	0.570 (0.515–0.624)
			Factor	0.5645 (0.2247)			

Table 1. *(Cont'd)*

Variable	Summary statistics		ULR				
	Cases (n = 103)	Noncases (n = 365)	Parameter	Coefficient estimate (SE)	OR (95% CI)	*P*†	ROC AUC (95% CI)
Other clinical characteristics (bundle 4)							
Both hands abnormal on Allen test, n/N (%)	32/95 (33.7)	85/338 (25.1)	Intercept	−0.9768 (0.2074)	0.661 (0.405–1.081)	0.099	0.543 (0.490–0.596)
			Factor	−0.4135 (0.2507)			
Presence of paronychia, n/N (%)‡	20/103 (19.4)	38/365 (10.4)	Intercept	−1.3588 (0.1231)	2.048 (1.132–3.705)	0.018	0.545 (0.503–0.586)
			Factor	0.7170 (0.3024)			
Presence of pitting scars, n/N (%)	60/103 (58.3)	182/365 (49.9)	Intercept	−1.4815 (0.1752)	1.498 (0.958–2.342)	0.076	0.550 (0.496–0.604)
			Factor	0.4043 (0.2279)			

* Data are summary statistics of clinical covariables selected and carried forward to the multivariable logistic regression (MLR) within-bundle analysis in patients who developed (cases) and those who did not develop (noncases) a digital ulcer (DU) during the observation period. ULR = univariable logistic regression; 95% CI = 95% confidence interval; RP = Raynaud's phenomenon; MRSS = modified Rodnan skin thickness score.
† By Wald's chi-square test.
‡ Variable was also carried forward to the MLR across-bundles analysis.
§ Integrates the component variables of smoking intensity, smoking duration, and time since smoking cessation into a single covariate of smoking effect (61).
¶ The odds ratio (OR) is not given since the functional relationship is quadratic. The associated *P* value and receiver operating characteristic (ROC) area under the curve (AUC) are quadratic terms.
# For limited cutaneous systemic sclerosis (SSc) versus diffuse cutaneous SSc.
** For 1 DU versus 0 DUs.
†† For 2 DUs versus 0 DUs.
‡‡ For ≥3 DUs versus 0 DUs.

Table 2. NVC covariables selected at the ULR analysis stage and carried forward to the MLR within-bundle analysis in the DU history group*

Variable	Summary statistics: Cases (n = 103)	Summary statistics: Noncases (n = 365)	ULR: Parameter	ULR: Coefficient estimate (SE)	ULR: OR (95% CI)	ULR: *P*†	ULR: ROC AUC (95% CI)
Quantitative NVC characteristics (bundle 5)							
Finger level: dominant hand, 4 individual fingers (sub-bundle 5.5)‡							
Index finger, mean ± SD/mm; n							
No. of capillaries	3.9 ± 2.2; 89	4.5 ± 2.3; 325	Intercept	−0.7504 (0.2573)	0.879 (0.787–0.981)	0.022	0.603 (0.538–0.668)
			Linear	−0.1294 (0.0564)			
No. of microhemorrhages§	0.1 ± 0.4; 89	0.2 ± 0.5; 325	Intercept	−1.2157 (0.1270)	0.592 (0.305–1.150)	0.122	0.552 (0.512–0.593)
			Linear	−0.5239 (0.3386)			
Middle finger, mean ± SD/mm; n							
No. of capillaries§	3.8 ± 1.9; 97	4.7 ± 2.2; 339	Intercept	−0.3115 (0.2790)	0.801 (0.707–0.907)	<0.001	0.614 (0.553–0.674)
			Linear	−0.2217 (0.0634)			
No. of microhemorrhages	0.2 ± 0.8; 97	0.3 ± 0.6; 339	Intercept	−1.1172 (0.1247)	¶	0.007	0.565 (0.524–0.605)
			Linear	−1.6839 (0.5904)			
			Quadratic	0.5243 (0.1933)			
No. of neoangiogeneses§	0.6 ± 0.9; 97	0.4 ± 0.8; 339	Intercept	−1.4030 (0.1390)	1.326 (1.024–1.718)	0.032	0.558 (0.498–0.617)
			Linear	0.2823 (0.1319)			
Ring finger, mean ± SD/mm; n							
No. of capillaries	4.2 ± 2.1; 99	4.6 ± 2.1; 343	Intercept	−0.7917 (0.2677)	0.902 (0.807–1.009)	0.070	0.564 (0.500–0.629)
			Linear	−0.1031 (0.0570)			
Little finger, mean ± SD/mm; n							
No. of capillaries	4.1 ± 1.8; 97	5.0 ± 2.1; 347	Intercept	−0.3062 (0.2920)	0.808 (0.715–0.913)	<0.001	0.620 (0.558–0.681)
			Linear	−0.2137 (0.0624)			
Qualitative NVC characteristics (variable not included in a bundle)#							
NVC pattern at enrollment, n/N (%)							
Normal	0/103 (0.0)	4/363 (1.1)					0.597 (0.548–0.647)
Early	4/103 (3.9)	40/363 (11.0)					
Active	25/103 (24.3)	123/363 (33.9)	Intercept	−2.3972 (0.5221)	2.234 (0.736–6.779)**	0.156**	
			Factor	0.8039 (0.5663)			
Late	74/103 (71.8)	196/363 (54.0)	Factor	1.4231 (0.5396)	4.150 (1.441–11.950)††	0.008††	

* Data are summary statistics of nailfold videocapillaroscopy (NVC) covariables selected and carried forward to the multivariable logistic regression (MLR) within-bundle analysis in patients who developed (cases) and those who did not develop (noncases) a digital ulcer (DU) during the observation period. Quantitative NVC characteristics carried forward to the MLR within-bundle and across-bundles analyses for sub-bundles 5.1–5.4 and sub-bundle 5.6 are shown in Supplementary Table 5 (in section 3 of the Supplementary Materials, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). ULR = univariable logistic regression; 95% CI = 95% confidence interval.

† By Wald's chi-square test.

‡ The mean value at the finger level is the mean count per measurement from 2 capillaroscopic images.

§ Variable was also carried forward to the MLR across-bundles analysis.

¶ The odds ratio (OR) is not given since the functional relationship is quadratic. The associated *P* value and receiver operating characteristic (ROC) area under the curve (AUC) are quadratic terms.

Used in an alternative final model as a "surrogate" for NVC quantitative variables.

** Active versus normal/early pattern.

†† Late versus normal/early pattern.

Table 3. Medication use and relationship to DU disease severity*

Medication class	Summary statistics		*P* for association with DU disease severity	
	No. (%) of cases (n = 103)	No. (%) of noncases (n = 365)	No. of DUs (n = 468)†	Hospitalization due to DUs (n = 468)‡
At least 1 medication class	97 (94.2)	343 (94.0)	–	–
Vasoactive medication				
Endothelin receptor antagonists	43 (41.7)§	113 (31.0)	0.0251	0.0856
Phosphodiesterase 5 inhibitors	15 (14.6)	31 (8.5)	0.0088	0.8604
Prostanoids, including intravenous formulation	54 (52.4)§	140 (38.4)	0.3159	<0.0001
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	27 (26.2)	112 (30.7)	0.3283	0.5535
Calcium-channel blockers	57 (55.3)	206 (56.4)	0.1044	0.0553
Selective serotonin reuptake inhibitors	11 (10.7)	39 (10.7)	0.1935	0.0192
Nitrates	3 (2.9)	15 (4.1)	0.9737	0.7506
Statins	10 (9.7)§	69 (18.9)	0.0568	0.1097
Other vasodilators	10 (9.7)	53 (14.5)	0.3635	0.1534
Platelet aggregation inhibitors	39 (37.9)	163 (44.7)	0.1265	0.2490
Immunosuppressants	53 (51.5)§	139 (38.1)	0.1989	0.7551

* Includes ongoing medication use and medication use within 3 months prior to and at enrollment. DU = digital ulcer.
† By Cochran-Armitage trend test.
‡ By chi-square test.
§ $P < 0.05$ versus noncases, by chi-square test and Fisher's exact test.

clinical consensus (see Supplementary Table 8, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract).

The pattern of medication use (by class) varied from one country to another, and patients took a wide range of combinations from the different medication classes. An analysis showed that medication use within 3 months prior to and at enrollment was associated with DU disease severity prior to and at enrollment (number of DUs, by Cochran-Armitage trend test, and previous hospitalizations due to DUs, by chi-square test) (Table 3). Specifically, DU disease severity and medication use were collinear, meaning that one could be predicted from the other with reasonable accuracy. Therefore, due to the collinearity in the multivariable regression and the complexity of medication use patterns across the countries, it was decided to not include medication use as a potential risk factor, but to instead include DU disease severity in the model-building process.

Statistical criteria for selecting good-performing covariables via forward stepwise selection (FSS) at the ULR stage were the Wald's chi-square test statistic, $P < 0.15$ for linear terms, or $P < 0.05$ for quadratic terms. Categorical variables with a frequency of <20 patients were not moved forward from ULR to MLR (see Supplementary Table 9, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). In addition to FSS, the nominal group technique was used by the steering committee to exclude some covariables based on lack of clinical plausibility and/or feasibility, with particular regard to use in standard practice (see Supplementary Table 10). Statistical criteria for selecting covariables via FSS during MLR stage 2 (within-bundle) analysis were to enter if $P < 0.15$ and retain if $P < 0.10$. At MLR stage 3 (across-bundles) analysis, statistical criteria for selecting covariables via FSS were to enter if $P < 0.15$ and retain if $P < 0.05$. The reduction of covariables at each of the 3 stages resulted in the final MLR model.

Modeling within each of the NVC sub-bundles resulted in 6 competing MLR models. In order to retain only 1 type of NVC assessment in the final model from among the several assessment options for the NVC (qualitative or quantitative [on the patient, hand, and finger levels]), it was decided to carry forward the sub-bundle with the highest ROC AUC into the across-bundles stage.

Model validation. Internal validation of the final MLR model was performed through the bootstrap method (35), with 2,000 re-samples using the same model-building and covariable selection procedures as for the final model.

SAS software, version 9.1.3, was used for the statistical analysis and the reporting of clinical data.

RESULTS

Findings in the study population. DU outcome was known for 591 of the 623 enrolled patients. Among those 591 patients, 468 (79.2%) belonged to the DU history group (Figure 1), of whom 103 (22.0%) developed a DU during the observation period. Of the 123 patients in the no DU history group, only 5 (4.1%) developed a new DU (Figure 1). As the incidence of new DUs in the no DU history group was low, this report focuses on the DU history group. The distribution of the total number of patients and the number of patients who developed a new DU (cases) were highly variable across countries and centers (see Supplementary Figure 2, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). The results of the covariable selection process for the best-performing risk factors for new DU outcome for each bundle at stages 1, 2, and 3 of model development are presented in detail in Supplementary Tables 1–6.

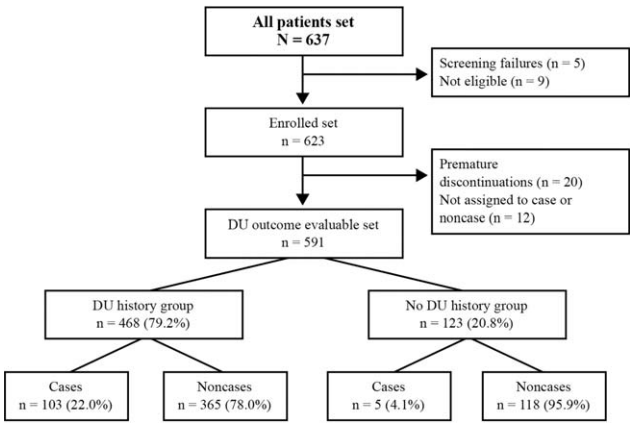

Figure 1. Flow chart showing the distribution of the study patients and stratification of the digital ulcer (DU) outcome set. In total, 637 patients with systemic sclerosis were screened. After exclusion of screening failures, ineligible patients, premature discontinuations, and patients not assigned to case or noncase categories, the DU outcome evaluable set (n = 591) was obtained. Because the variables that influence the occurrence of a new DU were thought to be different in the DU history group (those with a history of DUs or with DUs at enrollment) versus the no DU history group (those without a history of DUs), the data analysis was stratified in the same two study arms.

Demographic features, digital ulcers, and clinical characteristics. Of the DU history group, 79.5% of patients were female, 280 (59.8%) were classified as having limited cutaneous SSc, and 188 (40.2%) as having diffuse cutaneous SSc. The demographic, DU, and clinical characteristics, according to DU outcome, are reported in Table 1. The presence and number of DUs at enrollment were significantly associated with the occurrence of new DUs ($P < 0.001$), with the ORs increasing with an increasing number of DUs at enrollment. The OR of having a new DU was 2.691 (95% CI 1.507–4.803) in patients with 1 DU at enrollment, 3.787 (95% CI 1.879–7.630) in those with 2 DUs, and 7.399 (95% CI 3.687–14.848) in those with ≥3 DUs.

The ROC AUCs for individual non-NVC covariables by ULR (stage 1) had a range between 0.520 and 0.678 (Table 1). The highest ROC AUC for the non-NVC covariables selected by MLR within-bundle (stage 2) was for the DU characteristics bundle, at 0.694 (95% CI 0.637–0.751) (see Supplementary Tables 11–14, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). Calcinosis was present in 20.4% of cases and 18.4% of noncases. On ULR analysis, calcinosis was not significantly associated with the development of new DUs (OR 1.090 [95% CI 0.637–1.866]).

The vasomodulating and immunosuppressive medications taken during the 3 months prior to or at enrollment and their association with DU disease severity, are described in Table 3. During the observation period, medication use was stable for the drug classes recorded.

NVC covariables, qualitative and quantitative measurements. Descriptive analysis of the NVC covariables selected at the ULR stage and carried forward to the MLR within-bundle analysis, are reported in Table 2 and in Supplementary Tables 5 and 6. The NVC pattern was significantly associated with the DU outcome ($P < 0.002$); the proportion of patients with a late SSc NVC pattern was higher in the cases than in the noncases (71.8% versus 54.0%), and the OR for a late versus normal/early SSc NVC pattern was 4.150 (95% CI 1.441–11.950), which is consistent with previous reports (20,21). The mean number of capillaries per millimeter was significantly reduced in cases versus noncases regardless of the NVC quantitative assessment type used (patient, hand, or finger level).

The NVC covariables selected by MLR within-bundle analysis (stage 2) are depicted in Supplementary Tables 15 and 16 (available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). The NVC sub-bundle encompassing analysis at the finger level of the dominant hand in the 4 individual fingers (sub-bundle 5.5) had the highest ROC AUC among the 6 competing NVC sub-bundle models (ROC AUC 0.677 [95% CI 0.614–0.740]) and was carried forward to the MLR across-bundles analysis (stage 3). The complete list of NVC covariables carried forward from MLR within-bundle to MLR across-bundles analysis is presented in Supplementary Table 17 (available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract).

Interactions between covariables. Analysis of the interactions bundle 6 showed that none of the 8 interaction terms were statistically significant. Therefore, no interaction terms were carried forward to the MLR across-bundles analysis.

Non-NVC and NVC covariables in MLR across-bundles analysis. MLR across-bundles analysis (stage 3) resulted in the final model with 3 risk factors: 1) the mean number of capillaries/mm in the middle finger of the dominant hand (evaluated on 2 adjacent fields in the middle of the nailfold), with an OR of 0.838 (95% CI 0.735–0.955), 2) the number of DUs at the enrollment visit (categorized as 0, 1, 2, or ≥3), with an OR for ≥3 DUs versus 0 DUs at enrollment of 6.160 (95% CI 2.999–12.653), and 3) the presence of critical digital ischemia at enrollment, with an OR of 3.194 (95% CI 1.284–7.945) (Table 4). The ROC AUC for the model was 0.738 (95% CI 0.681–0.795), and the trade-off between sensitivity and specificity can be seen in the crossover curves (see Supplementary Figure 3, available online at http://onlinelibrary.wiley.com/doi/10.1002/art.39718/abstract). The Hosmer-Lemeshow test indicated that the final model did not show a significant lack of fit ($P = 0.751$). Internal validation of the final

Table 4. Final multivariable logistic regression model*

Variable	Coefficient estimate	MLR			
		Standard error	Odds ratio (95% CI)	Wald's chi-square test	*P*
Intercept	−1.0864	0.3299	0.337 (0.177–0.644)	10.8445	0.0010
Mean no. of capillaries/mm in middle finger of dominant hand	−0.1770	0.0670	0.838 (0.735–0.955)	6.9801	0.0082
No. of DUs at enrollment					
1	0.7460	0.3307	2.109 (1.103–4.032)	5.0878	0.0241
2	1.1696	0.3889	3.221 (1.503–6.902)	9.0458	0.0026
≥3	1.8181	0.3672	6.160 (2.999–12.653)	24.5082	<0.0001
Critical digital ischemia present at enrollment	1.1613	0.4649	3.194 (1.284–7.945)	6.2388	0.0125

* The final prognostic model used 3 variables to predict the occurrence of digital ulcers (DUs) within 6 months: the mean number of capillaries/mm in the middle finger of the dominant hand, the number of DUs at enrollment (categorized as 0, 1, 2, or ≥3), and the presence/absence of critical digital ischemia (defined as prolonged, severe, persistent reduction in digital tissue perfusion without rewarming) at enrollment. The multivariable logistic regression (MLR) coefficient estimates indicate that the risk of developing a DU within 6 months increases in patients with critical digital ischemia at enrollment, in patients with a greater number of DUs, and in patients with a lower number of capillaries/mm in the middle finger of the dominant hand. No variable among the demographic, SSc clinical, or other clinical characteristic bundle was retained. Receiver operating characteristic curve analysis showed an area under the curve of 0.738 (95% confidence interval [95% CI] 0.681–0.795). The Hosmer-Lemeshow goodness-of-fit test yielded the following values: $\chi^2 = 5.0602$, 8 df, $P = 0.751$. The MLR equation, based on the estimates shown in the table, was as follows:

$$\text{Probability of new DUs within 6 months} = \exp(\text{linear predictor})/[1 + \exp(\text{linear predictor})]$$

where the linear predictor is −1.0864 (intercept) −0.1770 multiplied by the mean number of capillaries per mm in the middle finger of the dominant hand, plus either 0.7460 for the presence of 1 DU, 1.1696 for 2 DUs, or 1.8181 for ≥3 DUs at enrollment, plus 1.1613 for the presence of critical digital ischemia at enrollment. Thus, a patient with 5 capillaries/mm in the middle finger of the dominant hand, plus 2 DUs at enrollment, plus critical digital ischemia at enrollment has a 59% probability of developing new DUs within 6 months.

MLR model through bootstrap generated a ROC AUC of 0.633 (95% CI 0.510–0.756).

A supplementary analysis in which the NVC pattern was used as the NVC covariable in the final model yielded similar model performance, with a ROC AUC of 0.715 (95% CI 0.658–0.771).

DISCUSSION

The CAP study was the first large, prospective, international, multicenter study to evaluate capillaroscopic and other clinical characteristics to determine risk factors for the development of new DUs during a 6-month period in patients with SSc. A very low number of cases were reported in the no DU history group during the 6-month observation period; therefore, risk factor analysis was performed only on the DU history group. The strongest performing risk factors for the occurrence of new DUs identified by MLR analysis were the mean number of capillaries per millimeter in the middle finger of the dominant hand, the number of DUs at enrollment, and the presence of critical digital ischemia at enrollment.

The characteristics of our study population were similar to those in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research Group (EUSTAR) cohort of patients with SSc (36). As expected, it appeared that the number of DUs had a large influence on the risk of future DUs, which is consistent with data reported previously (37,38), and may be linked to increased severity of SSc disease, since patients with DUs are more likely to have an earlier onset of SSc and more extensive skin involvement (3). There are a number of therapies available for the prevention of DUs (32,39,40), and it is therefore important to identify patients who are at risk of developing DUs so that they can receive preventive management.

Consistent with previous studies, the CAP study revealed capillary density (number of capillaries/mm) as the most robust NVC risk factor for new DUs. Of note, loss of capillaries has been linked to an increased risk of developing SSc and may therefore predict an early diagnosis, more severe skin involvement, and a poorer prognosis (21,41–46). While the current study found that the capillary density on the third digit of the dominant hand was sufficient for predicting the risk of new DUs, it is still necessary to evaluate at least 4 digits per hand for the diagnosis of SSc in patients with Raynaud's phenomenon. The study also indicated that the NVC pattern may play a role in predicting DUs, confirming the results of smaller studies that have shown that the late SSc NVC pattern is associated with an increased risk of DUs (20,47,48). Ideally, future studies would encompass NVC-based indices assessing

eventual disease-modifying characteristics of treatment on the clinical complications of SSc such as DUs (49,50).

With regard to the individual performance of each of the final model's 3 variables in the ULR analysis, the number of DUs was the strongest risk factor (ROC AUC 0.678), followed by the number of capillaries/mm in the middle finger of the dominant hand (ROC AUC 0.614), and then the presence of critical digital ischemia at enrollment (ROC AUC 0.556). The combination of the 3 variables in the final MLR model improved the model's discriminatory ability (ROC AUC 0.738). Furthermore, the relative weights of the Wald's chi-square values for the 3 variables (Table 4) demonstrated that both the number of capillaries/mm in the middle finger of the dominant hand (NVC variable) and critical digital ischemia at enrollment make important additional contributions to the number of DUs for determining the risk of new DUs in the final MLR model.

Interestingly, whereas a 50% incidence of new DUs in the DU history group had been assumed in the sample size estimation of our study, in reality, there was only a 22% incidence. The lower-than-expected incidence of new DUs may be the result of patients already receiving best practice standard of care for the management of their disease at enrollment. Medication use was not restricted, varied between countries, and was found to be associated with DU disease severity, which is consistent with findings from the Digital Ulcer Outcome Registry showing that patients with chronic and/or recurrent DUs have a shorter time to new DUs as compared with patients with no or episodic DUs (51). Therefore, medication use was not considered to be an independent variable and was not included as a potential risk factor for new DUs.

Because the no DU history subgroup was considered exploratory, it was not possible to identify variables that predicted DUs because of the small number of cases in this subgroup. We had anticipated at least 20% of cases, based on the report that 50% of patients with SSc experience DUs (1) and the fact that the first DU usually occurs early in the disease course (3); however, we observed only 4.1% of cases of new DUs in this subgroup. This may have 2 explanations. First, the SSc population may have changed in the last few years: patients with SSc may be diagnosed earlier than in the past, and preventive and efficient measures are now more widely used. Second, it might have been beneficial to restrict patients in the no DU history group to those with a first non–Raynaud's phenomenon symptom within 1 year (instead of 2 years) in order to be closer to the population described by Hachulla et al (3), in which 43% of patients had their first DU within 1 year of their first clinical sign of SSc.

NVC has the potential to be a useful tool for monitoring the progression of microvascular disease associated with SSc and for measuring the response to treatment (52,53). It is a well-established, noninvasive technique that allows for higher-magnification analysis compared with the older widefield capillaroscopic method (53,54). The training needed for the device is minimal (~5 days [55]) and the required examination time is short (~10 minutes including image recording). An NVC apparatus is more costly than handheld devices such as dermatoscopes, but NVC has been shown to permit more-detailed assessments (56) and the grading of more images (54). During patient follow-up, detailed assessment and quantification of abnormalities is important, and therefore, handheld tools may not be as useful in this setting (53). Of note, capillaroscopy has been recently introduced as a criterion in the ACR/EULAR classification criteria for SSc (16), thereby increasing their sensitivity and specificity.

Overall, there are several key strengths of this study. First is its generalizability, ensured by the broad distribution of participating centers and patients representing current standard of care. Second is its applicability in real-world clinical practice, owing to the broad study population, the simplicity and ease of clinical evaluation of the NVC, and the clinical risk factors that built the final model. Third is its value in the management of patients with a history or presence of DUs. The scope of the CAP study was to determine risk factors for developing DUs by using NVC and other clinical characteristics in routine clinical practice and health care environments, including centers with different levels of NVC experience. Thus, the "center" was not regarded as a potential risk factor, which could allow generalizability of the study findings for patients with SSc outside of the study centers. The interrater variability of NVC assessments has been of concern, and the capillary density has been identified as the NVC variable with the best interrater agreement in earlier, smaller studies (28,57). In the CAP study, interrater variability was addressed by practical training and teaching booklets that were offered to the investigators. Despite these efforts, the ambitious intention to allow extrapolation to the real-world setting may have introduced a large amount of noise that was detrimental to obtaining a final model with high discriminatory ability.

Limitations of this study include the fact that the diagnosis of DUs and critical digital ischemia is not always unequivocal (58,59), although definitions were provided in the protocol and/or the case report form. Investigators were not blinded to the NVC and other clinical characteristics assessed at enrollment and may therefore have been biased in favor of a diagnosis of a new DU. However, this was inherent to the real-world nature of the study, as physicians in clinical practice are not blinded to the results of other assessments.

Although the wide geographic spread of centers permits generalizability, it was conducive to introducing heterogeneity in the data. The center effect could not be explored in depth because of the wide distribution of patients across a large number of centers, with a small number of cases per center. Although it was estimated that 150 cases would be a reasonable number for exploring risk factor associations with the development of DUs, only 103 cases were observed in this cohort and, as such, the study was underpowered. Nevertheless, the modeling strategy (ULR, MLR within-bundle, MLR across-bundles analyses), together with the reduction in the number of variables entered into the model and the bootstrap validation demonstrated the robustness of the variables in the final model, thereby compensating for the lower-than-prespecified number of cases.

Laboratory biomarkers were not included in this study, which could have helped to improve the discriminatory ability of the final model. Biomarkers have previously been shown to be useful for predicting DUs (60) and may be useful to include in future studies. Given the nature of this real-world observational study, it was not feasible to determine the presence of an association between medication use and development of DUs. Future larger studies could be designed to explore this association by controlling for confounding factors such as DU disease severity and the use of medications (individually and in combination) in different countries.

In conclusion, this longitudinal, multicenter study of almost 500 patients with SSc has shown that the mean number of capillaries/mm on the middle finger of the dominant hand, the number of DUs at enrollment, and the presence of critical digital ischemia at enrollment are risk factors for the development of new DUs. The risk factors identified are simple to evaluate in the clinic, and the real-world nature of the study allows the results to be generalized to a wider SSc population, thereby providing the physician with useful information when considering a patient's risk of future DUs.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Cutolo and Smith had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cutolo, Herrick, Distler, Chadha-Boreham, Cottreel, Pfister, Rosenberg, Smith.

Acquisition of data. Cutolo, Herrick, Distler, Beltran, Carpentier, Inanç, Vlachoyiannopoulos, Smith.

Analysis and interpretation of data. Cutolo, Herrick, Distler, Becker, Beltran, Carpentier, Ferri, Inanç, Vlachoyiannopoulos, Chadha-Boreham, Cottreel, Pfister, Rosenberg, Torres, Smith.

ROLE OF THE STUDY SPONSOR

Actelion Pharmaceuticals funded the study and was responsible for the study protocol design, data collection, and statistical analysis, with, and under the leadership of, an independent study steering committee (non-Actelion authors). Actelion Pharmaceuticals also paid for editorial assistance (provided by Drs. Marion James and Lynda McEvoy, ApotheCom, a medical communications company). The steering committee members, all of whom are authors of this article, and the 4 authors employed by Actelion Pharmaceuticals were involved in the decision to submit the article for publication. Publication of this article was not contingent upon approval by Actelion Pharmaceuticals.

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